

Agenda
Meeting of the Developmental and Reproductive Toxicant
Identification Committee

December 13, 1999
2020 L Street, Air Resources Board, Board Room Lower Level, Sacramento

Meeting Chair: Dr. Dorothy Burk, Vice-Chair,
Developmental and Reproductive Toxicant (DART) Identification Committee

I. INTRODUCTION – OPENING REMARKS

Dr. Joan Denton, Director, Office of Environmental Health Hazard Assessment (OEHHA)

II. CONSIDERATION OF CHEMICALS KNOWN TO CAUSE REPRODUCTIVE TOXICITY

A. Quizalofop ethyl

- Staff presentation (Dr. Jim Donald, OEHHA)
- Committee discussion
- Public comments
- Committee discussion and decision

B. Fenbutatin oxide

- Staff presentation (Dr. Jim Morgan, OEHHA)
- Committee discussion
- Public comments
- Committee discussion and decision

III. STAFF UPDATES

- Chemicals added via the administrative listing mechanism (Cynthia Oshita, OEHHA)
- Proposition 65 litigation and rulings (Colleen Heck, OEHHA)
- Public Comment

IV. SUMMARY OF COMMITTEE ACTIONS – CLOSING REMARKS

Dr. Joan Denton, Director, OEHHA

**OEHHA Staff Transparencies from Meeting:
Developmental and Reproductive Toxicant Identification Committee
Held on December 13, 1999**

A meeting of the Developmental and Reproductive Toxicant (DART) Identification Committee was held on December 13, 1999, at the 2020 L Street, Air Resources Board in Sacramento, California. Below are the transparencies of presentations made by staff of California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA). The segments of the agenda covered with this material include the "Consideration of Chemicals Known to Cause Reproductive Toxicity." The DART Identification Committee determined that quizalofop-ethyl was clearly shown to cause male reproductive toxicity.

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EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF FENBUTATIN OXIDE

REPRODUCTIVE AND CANCER HAZARD
ASSESSMENT SECTION
OFFICE OF ENVIRONMENTAL HEALTH HAZARD
ASSESSMENT
DECEMBER 13, 1999

EVIDENCE ON DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF QUIZALOFOP-ETHYL

REPRODUCTIVE AND CANCER HAZARD
ASSESSMENT SECTION
OFFICE OF ENVIRONMENTAL HEALTH HAZARD
ASSESSMENT
DECEMBER 13, 1999

Basis for Consideration of Quizalofop ethyl

- Formal identification by the U.S. Environmental Protection Agency as causing (male) reproductive toxicity
- After publication of a Notice of Intent to List, referred to the DART Committee because the data used by the authoritative body did not meet the criteria specified in regulations

Quizalofop-ethyl

- Phenoxypropionic acid ester
- [(2-(4-((6-chloro-2-quinoxalinyloxy)phenoxy)-ethyl ester)]
- $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}_4$ (Molecular weight 372.81)

Uses

- Formerly used as a herbicide on broadleaf crops
- Not registered for use in California since 1993

Developmental effects

- Human data: none identified
- Animal data: 3 studies
- *Rabbits: 1 study*
 - * orally exposed on days 6-18 of gestation,
no adverse developmental effects
(high dose mildly toxic to the dams)

Developmental effects (cont.)

- *Rats: 2 studies*
- Developmental toxicity study
 - * orally exposed on days 6-15 of gestation
 - * lower fetal survival at day 21 at the highest dose tested ($p < 0.05$)
 - * higher incidence of skeletal variations at the high ($p < 0.001$) and mid ($p < 0.05$) doses

Developmental effects (cont.)

- Developmental toxicity study (continued)
 - * lower postnatal bodyweight and food intake in high dose offspring
 - * lower absolute ($p < 0.01$) and relative ($p < 0.05$) uterine weights in high dose female offspring at age 8 weeks
 - * No effects on reproductive function at age 10 weeks in animals treated *in utero*

Developmental effects (cont.)

- 2-generation reproductive toxicity study
 - * decreased percentage or number of pups born alive in the F_{1A} and F_{2A} high-dose litters
 - * decrease birthweights in the high-dose litters in the F_{1A} and F_{1B} groups
 - * decrease early postnatal weights in the high-dose litters in the F_{1A} , F_{1B} and F_{2B} groups

Developmental effects (cont.)

- 2-generation reproductive toxicity study (continued)
 - * increased incidence of hemangioma in all treatment groups (F_{1B} generation) and the mid- and high-dose groups (F_{2A} generation)

Female reproductive effects

- Human data: none identified
- Animal data:
- One 2-generation reproductive toxicity study in rats, one study in rats of effects of *in utero* exposure on reproductive function
- Five studies of potential reproductive organ effects

Female reproductive effects (cont.)

- *Rats: 2-generation reproduction study*
 - * Significant decrease in fertility index in low-dose dams of the F_{1A} generation (no effect on mid- and high-dose dams in this generation, no effect on any dose groups in other generations)

Female reproductive effects (cont.)

- *Dogs: 2 subchronic studies*
 - * uterine and ovarian weights varied from control values, no apparent dose-response relationship
- *Rats: 2 subchronic/chronic studies*
 - * no evidence of effects on female reproductive organs

Female reproductive effects (cont.)

- *Mice: 1 chronic study*
 - * uterine and ovarian weights increased at all doses tested
 - * increased incidence of ovarian hemorrhage at the high dose tested

Male reproductive effects

- Human data: none identified
- Animal data:
- One 2-generation reproductive toxicity study in rats, one study in rats of effects of *in utero* exposure on reproductive function
- 5 studies of potential reproductive organ effects

Male reproductive effects (cont.)

- *Rats: 2-generation reproduction study*
 - * Significant decrease in fertility index in low-dose males of the F_0 generation (no effect on mid- and high-dose males in this generation or the F_{1A} generation)
 - * Single incidence of focal hyperplasia of the testis in a high-dose male in the F_{1A} group

Male reproductive effects (cont.)

- *Dogs: 2 subchronic studies*
 - * 6 month study; testicular atrophy reported at high dose tested (basis for authoritative body identification of reproductive toxicity)
 - * 12 month study; same design as above, more comprehensive assessment of testes did not identify any testicular atrophy

Male reproductive effects (cont.)

- *Rats: 2 studies*
 - * 13 week study; high incidence of testicular atrophy at end of treatment and also after a 6 week recovery period
 - * 104 week study; no testicular atrophy after exposure to approximately one third the effective dose in the earlier study

Male reproductive effects (cont.)

- *Mice: 1 chronic study*
 - * 78 week study; increased incidence of testicular atrophy.
 - * Bilateral atrophy increased in dose-related manner at two highest doses.
 - * Combined unilateral and bilateral atrophy increased at all doses

Summary

- **Evidence for developmental toxicity of quizalofop-ethyl**
- *Developmental toxicity study (rats exposed on days 6-15 of gestation):*
 - lower fetal survival
 - higher incidence of skeletal variations

Summary (cont.)

- *Developmental toxicity study (rats exposed on days 6-15 of gestation) (continued):*
 - lower postnatal bodyweight and food intake
 - lower absolute and relative uterine weights at 8 weeks of age

Summary (cont.)

- *2-generation reproductive toxicity study (rats):*
 - decreased live births, birthweights and early postnatal weights
 - increased incidence of hemangioma in pups

Summary (cont.)

- **Evidence for female reproductive toxicity of quizalofop-ethyl:**
 - increased ovarian weights and increased incidence of ovarian hemorrhage after 78 weeks exposure in mice

Summary (cont.)

- **Evidence for male reproductive toxicity of quizalofop-ethyl:**
 - testicular atrophy in dogs exposed to quizalofop-ethyl for 6 months (but not in dogs exposed for 12 months)
 - increased incidence of testicular atrophy in rats exposed for 13 weeks

Summary (cont.)

- increased incidence of testicular atrophy in mice exposed for 78 weeks
- isolated decrease in fertility index in low-dose males of the F_0 generation only in a 2-generation reproduction study
- single incidence of focal hyperplasia of the testis in an F_1 rat from a 2-generation reproduction study

Fenbutatin Oxide

- Large organotin pesticide (MW 1052.7 D)
- Insoluble in water
- Somewhat soluble in aromatic solvents
- Used as miticide on fruits, vegetables, nuts, flowers
- Poorly absorbed orally: approximately 1% in rats, cows
- Acute toxicity: oral LD₅₀ in rats 4400 mg/kg
- Chronic toxicity: typically reduced body weight (e.g. rats at 300 ppm in food)

Studies with possible evidence of developmental effects

- No human data
- Rat developmental study (Shell 1980b)*
- Dutch rabbit developmental studies A and B (Shell 1973a)
- New Zealand White rabbit developmental study (Shell 1981)*
- Rat reproductive study (3-gen., 2 litter/gen., male and female treated) (Hine Laboratories 1973)*
- Rat reproductive study (2-gen., 1 litter/gen., male and female treated) (du Pont 1990)

* cited by U.S. EPA

Rat developmental study (Shell 1980b)

- Mated Wistar rats treated at 0, 15, 30, or 60 mg/kg/d on gd 6-15 by gavage, sacrificed on gd 20

Effects observed:

- Reduced pregnancies at 30, 60 mg/kg/d (SS at 30, marginal SS at 60)
- Increased mean pre-implantation losses at 15, 60 mg/kg/d (SS at 60)
- No effect live fetuses/litter

Additional considerations:

- Implantation occurs on gd 5-6, treatment began gd 6
- No dose response of reduced pregnancies or mean pre-implantation losses
- “Negative” pre-implantation losses in some animals (more implants than corpora lutea counted)

Dutch rabbit developmental studies (Shell 1973a)

- Mated Dutch rabbits treated at 0, 3, or 10 mg/kg/d on gd 6-18 by capsule, sacrificed on gd 28 (Study A)

Effects observed:

- Increased resorptions plus early fetal deaths and fetuses with major abnormalities at 3, but not 10 mg/kg/d
- Large numbers of maternal deaths, apparently randomly distributed among groups

Additional considerations:

- Lack of dose-response for resorptions plus fetal deaths, abnormalities
- Lack of statistical analysis for resorptions plus fetal deaths, abnormalities

Dutch rabbit developmental studies (Shell 1973a)

- Mated Dutch rabbits treated at 0, 3, or 10 mg/kg/d on gd 6-18 by capsule, sacrificed on gd 29 (Study B)

Effects observed:

- Small, dose-related increase in resorptions plus early fetal deaths at 3 and 10 mg/kg/d
- No increase in major malformations
- Large numbers of maternal deaths, apparently randomly distributed among groups

Additional considerations:

- Lack of statistical analysis for resorptions plus fetal deaths

New Zealand White rabbit developmental study (Shell 1981)

- Mated New Zealand White rabbits treated at 0, 1, 5, or 10 mg/kg/d on gd 6-18 by capsule, sacrificed on gd 29

Effects observed:

- 10 mg/kg/d: increased maternal deaths (5/23), reduced maternal weight (SS), increased abortions (60%: SS), increased post-implantation losses (not SS), reduced number of litters with live fetuses (SS)
- 5 mg/kg/d: maternal deaths (2/18), increased post-implantation losses (not SS)
- 1 mg/kg/d: no maternal deaths or other effects
- 0 mg/kg/d: 2/18 maternal deaths

Additional considerations:

- Thalidomide positive control: no maternal deaths

3-gen. rat reproductive study (Hine Labs 1973)

- Male and female Long-Evans rats treated at 0, 50, 100, 300 ppm in food for 3 generations with 2 litters/generation

Effects observed:

- Small, consistent reduction in litter size at 300 ppm (SS for F1b only)
- Reduced postnatal survival (to day 21) at 300 ppm in F3a, F3b (SS)
- Reduced postnatal weight (day 21) at 300 ppm (SS 5/6 litters)
- Reduced parental weights at 300 ppm (SS male 3/3, female 2/3)

Additional considerations:

- Reduced litter size not observed in later rat reproduction study
- Exposure before developmental period
- Pups may have been exposed postnatally (milk, food)

2-gen. rat reproductive study (du Pont 1990)

- Male and female Sprague-Dawley rats treated at 0, 45, 75, 250, or 500 ppm in food for 2 generations with 1 litter/generation

Effects observed:

- Reduced postnatal weight gain at 500 ppm, F1 and F2 (SS)
- Reduced parental weight gain (male and female) at 500 ppm, P1 and F1 (SS)

Additional considerations:

- Exposure before developmental period
- Pups may have been exposed postnatally (milk, food)

Studies with possible evidence of female reproductive effects

- No human data
- Rat reproductive study (3-gen., 2 litter/gen., male and female treated) (Hine Laboratories 1973)
- Rat reproductive study (2-gen., 1 litter/gen., male and female treated) (du Pont 1990)
- Rat acute inhalation (IBTL 1972a, 1972b, 1972c)
- Rat, mouse, and dog chronic oral (Shell 1973b, 1973c, 1980a, U.S. EPA 1994)

No effects on fertility

- 3-generation rat reproductive study (Hine Labs 1973)
- 2-generation rat reproductive study (du Pont 1990)

No observations of ovarian gross or histopathological effects

- 2-generation rat reproductive study (du Pont 1990)
- Acute inhalation studies in rats (IBTL 1972a, 1972b, 1972c)
- Chronic studies in rats (Shell 1973b), mice (Shell 1980a, U.S. EPA 1994), or dogs (Shell 1973c)

Studies with possible evidence of male reproductive effects

- No human data
- Rat reproductive study (3-gen., 2 litter/gen., male and female treated) (Hine Laboratories 1973)
- Rat reproductive study (2-gen., 1 litter/gen., male and female treated) (du Pont 1990)
- Mouse dominant lethal study (Shell 1972)
- Rat acute inhalation (IBTL 1972a, 1972b, 1972c)
- Rat subchronic oral (SRI 1970)
- Rat, mouse, and dog chronic oral (Shell 1973b, 1973c, 1980a, U.S. EPA 1994)

Dominant lethal study in male mice (Shell 1972)

- Male mice treated at 0, 250, or 500 mg/kg once orally, mated with 3 untreated females each for one week, repeated for 8 weeks. Females examined on gd 13.

Effects observed:

- No adverse effects on number of pregnancies, total number of implants, early fetal deaths.

Additional considerations:

- Not clear if systemically toxic dose was used.

No effects on fertility

- 3-generation rat reproductive study (Hine Labs 1973)
- 2-generation rat reproductive study (du Pont 1990)
- Dominant lethal study in mice (Shell 1972)

No observations of testicular gross or histopathological effects

- 2-generation rat reproductive study (du Pont 1990)
- Acute inhalation studies in rats (IBTL 1972a, 1972b, 1972c)
- Subchronic study in rats (SRI 1970)
- Chronic studies in rats (Shell 1973b), mice (Shell 1980a, U.S. EPA 1994), or dogs (Shell 1973c)

Overview of rat testes weight effects

Inconsistent indications of increased testes weight in animals exposed when mature:

- Increased* absolute testes weight in 1-month study at 500, 1000 ppm
- Increased (SS) absolute testes weight at terminal sacrifice (24 months) in chronic study at 600 ppm
- No increase in absolute testes weight at 3, 6, or 12 months in chronic study to 600 ppm
- No increase in absolute testes weight after 18 weeks in P1 of 2-gen. to 500 ppm

Additional considerations

- Reduced body weight in all studies
- 15-week food restriction study (Chapin et al. 1993) in mature animals reduced to 90, 80, or 70% of control body weight:
no change in absolute testes weight,
increased relative testes weight due to reduced body weight

* Value calculated by OEHHA staff: SS not addressed

Overview of rat testes weight effects cont.

Indications of reduced testes weight in animals exposed during perinatal period:

- Reduced absolute* and relative (SS) testes weight in F3b weanlings (3 weeks old) at 100, 300 ppm in 3-gen.
- Reduced (SS) absolute testes weight, increased relative (SS) testes weight at term in F1 at 500 ppm in 2-gen.

Additional considerations

- Reduced body weight at 300 ppm in 3-gen., 500 ppm in 2-gen.

* Value calculated by OEHHA staff: SS not addressed

Summary: developmental

- Rat developmental study
Reduced pregnancies, increased pre-implant losses
- Rabbit developmental studies (3)
Increased post-implant losses, maternal deaths (random and dose-related)
- Rat 3-gen. study
Reduced litter size, reduced postnatal growth and survival, reduced parental weight
- Rat 2-gen. study
Reduced postnatal growth, reduced parental weight

Summary: female reproductive

- Rat 3-gen. study
No effect fertility. Reduced litter size, reduced postnatal growth and survival, reduced parental weight
- Rat 2-gen. study
No effect fertility. Reduced postnatal growth, reduced parental weight
- Rat, mouse, dog/acute, chronic
No ovarian gross or histopathology

Summary: male reproductive

- Rat 3-gen. study
No effect fertility. Reduced litter size, reduced parental weight
- Rat 2-gen. study
No effect fertility, litter size. Reduced parental weight
- Mouse dominant lethal study
No effect fertility, pre- or post-implantation losses
- Rat, mouse, dog/acute, subchronic, chronic, repro
No testicular gross or histopathology
- Rat testes weight effects:
mature: inconsistent increases in absolute testes weight
perinatal: indications of reduced testes weight